Effect of changes in oscillatory amplitude on Paco_2 and Pao_2 during high frequency oscillatory ventilation

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Abstract

Aims—To describe the relation between oscillatory amplitude changes and arterial blood gas (ABG) changes in preterm infants receiving high frequency oscillatory ventilation, using a multiparameter intra-arterial sensor (MPIAS).

Methods—Continuous MPIAS ABG data were collected after amplitude changes and stratified according to Fio_2 : high (> 0.4) or low (< 0.3). For each amplitude change, the maximum change (from baseline) in Paco_2 and Pao_2 over the following 30 minutes was determined. In total, 64 oscillatory amplitude changes were measured in 21 infants (median birth weight 1040 g; gestation 27 weeks).

Results—All amplitude increases produced Paco_2 falls (median -0.98 and -1.13 kPa for high and low Fio_2 groups respectively). All amplitude decreases produced Paco_2 rises (median $+0.94$ and $+1.24$ kPa for high and low Fio_2 groups respectively). About 95% of the change in Paco_2 was completed in 30 minutes. Amplitude changes did not affect Pao_2 when $\text{Fio}_2 > 0.4$. When $\text{Fio}_2 < 0.3$, amplitude increases produced a Pao_2 rise (median $+1.1$ kPa; $P < 0.001$) and amplitude decreases a fall (median -1.2 kPa; $P < 0.001$).

Conclusions—After oscillatory amplitude changes, the speed but not the magnitude of the Paco_2 change is predictable, and a rapid Pao_2 change accompanies the Paco_2 change in infants with mild lung disease and a low Fio_2 .

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Keywords: arterial; blood gas monitoring; lung; oscillatory amplitude; prematurity; ventilation

High frequency oscillatory ventilation (HFOV) is establishing itself as an effective alternative to conventional tidal volume ventilation in newborn infants with severe lung disease. Its potential benefit is ventilation at a lower peak airway pressure and Fio_2 , both of which may reduce lung injury. This has the potential to reduce air leak and chronic lung disease. These benefits have been shown in animal studies^{1–3} and clinical randomised controlled trials^{4–6} comparing elective or early HFOV and conventional ventilation.

The clinical studies showing benefit have used a “high lung volume strategy”. Oxygenation is controlled by changes in the Fio_2 and mean airway pressure. The high lung volume

strategy seeks to “recruit” lung volume by progressively increasing the mean airway pressure but avoiding hyperinflation. These increases in mean airway pressure and lung volume allow reductions in the Fio_2 . Thus the Fio_2 is used as a crude surrogate for lung volume recruitment. The aim is to achieve an $\text{Fio}_2 < 0.3$. This signals adequate lung volume recruitment and is associated with an increase in lung compliance. Static volume pressure curves during HFOV³ indicate that mean airway pressure can then be reduced without loss of lung volume. Ensuring adequate lung volume recruitment and avoiding hyperinflation is achieved with the aid of frequent chest radiographs. Subsequent weaning then involves reducing Fio_2 before further reductions in mean airway pressure. Oscillatory amplitude is used to control ventilation and therefore Paco_2 .

Oxygenation during HFOV is thought to be independent of frequency and tidal volume,⁷ except at very low values.⁸ Thus mean airway pressure and Fio_2 alone are used to determine oxygenation. Conversely, CO_2 elimination during HFOV is related to frequency and tidal volume and is thought to be independent of mean airway pressure.⁷ In clinical practice, changes in oscillatory amplitude (and only occasionally frequency) are mainly used to alter CO_2 elimination. These relations have important implications for the clinician using a high lung volume strategy during HFOV: the ventilator settings that determine oxygenation appear to be independent of those that govern CO_2 elimination.

We have recently completed a multicentre validation study of a multiparameter intra-arterial sensor (MPIAS) capable of continuous blood gas monitoring in the newborn infant.⁹ This has allowed us to make some novel observations about the acute arterial blood gas (ABG) changes that occur following changes in the ventilator settings during HFOV. In particular, we observed that the effect of changes in oscillatory amplitude appeared to differ during the disease process in the same infant and between infants with different disease severity.

Based on these initial observations, we have performed an observational study with the following aims:

- to describe the relation between changes in oscillatory amplitude and changes in Paco_2 and Pao_2 using the MPIAS;
- to compare effects of changes in oscillatory amplitude on ABG status at different severities of lung disease.

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Methods

The study received local ethics committee approval. Informed parental consent was given before randomised changes in ventilation were performed. All infants were studied at the neonatal intensive care unit, St James' University Hospital, Leeds. This unit has a policy of elective HFOV (Sensormedics, 3100A) in all infants under 28 weeks gestation. In addition, those infants receiving conventional ventilation, with radiological evidence of severe lung disease, peak inspiratory pressure exceeding 30 cm H₂O, or FIO₂ > 0.6 are switched to HFOV. Infants were managed according to the unit HFOV protocol, which is based on a high lung volume strategy.

In order to be eligible for study, subjects had to be preterm infants receiving HFOV, with an MPIAS in place and a clinical and radiological diagnosis of respiratory distress syndrome. Consequently, all infants had received at least one dose of surfactant and were more than 4 hours old. Infants in whom there was an identifiable (clinically and/or radiologically) additional cause of respiratory distress or congenital heart disease at the time of study were excluded.

The MPIAS (Neotrend; Diametrics Medical Ltd, High Wycombe, Bucks, UK) allows continuous monitoring of pH, Paco₂, and Pao₂.⁹ The cotside monitor displays continuous ABG status as a trend over time. Data can be displayed over time periods ranging from the previous 10 minutes to the previous 24 hours. ABG data can be retrieved at any time point available on the screen display. Hard copies of screen information can be printed when required.

Infants were managed using the unit's HFOV protocol, which indicates that the ideal is to maintain Paco₂ at 4.0–6.0 kPa and keep within 3.5–7.0 kPa (Pao₂ equivalents are 7–10 kPa and 6–12 kPa respectively). FIO₂ was set at a level to maintain Pao₂ at 7–10 kPa. Most changes in oscillatory amplitude were clinically determined and driven by the unit's HFOV protocol. Changes in oscillatory amplitude were made in increments of 2 or 3 cm H₂O. A small number of random changes in oscillatory amplitude (± 3 cm H₂O) were also studied. This was to ensure a full range of Paco₂ values at the time of the change in oscillatory amplitude. Random changes in oscillatory amplitude were only performed when the Paco₂ and Pao₂ were in the ideal ranges and had stable baselines.

Clearly, it was necessary to ensure, as far as possible, that acute ABG changes were the result of the change in oscillatory amplitude and not some other factor. The time at which the oscillatory amplitude was changed is referred to as t_0 . Data collection took place only when the change in amplitude met the following criteria:

- no other changes in ventilator settings;
- inspiratory time 30%, frequency 10 Hz;
- a period of stable Paco₂ and Pao₂ baselines before t_0 .

Paco₂ and Pao₂ baselines were defined as stable, before the time of each change in oscil-

latory amplitude (t_0), if they met one of the following criteria:

- no change in Paco₂ (± 0.1 kPa) and Pao₂ (± 0.2 kPa) for more than five minutes before t_0 ;
- no change in Paco₂ (± 0.3 kPa) and Pao₂ (± 0.5 kPa) for more than 30 minutes before t_0 ;
- consistent linear change had been present for more than 20 minutes before t_0 .

DATA COLLECTION

For each change in oscillatory amplitude the following basic data were collected:

- oscillatory amplitude, mean airway pressure, and FIO₂ immediately before t_0 ;
- change in oscillatory amplitude at t_0 ;
- lung inflation (posterior ribs) and grade of respiratory distress syndrome on last chest radiograph.

The minimum study period after t_0 was 30 minutes. Where possible, further data were collected at 10 minute intervals after the end of the study period (after t_{30}).

For each change in oscillatory amplitude, the following ABG data represent the minimum data set collected:

- Paco₂ and Pao₂ at t_0 ;
- Paco₂ and Pao₂ at 5, 10, 20, and 30 minutes after t_0 (t_5 , t_{10} , t_{20} , t_{30});
- direction of change of Paco₂ and Pao₂ established before t_5 (+ or – or 0);
- earliest time ($t_{\max30}$) at which maximum Paco₂/O₂ change (from baseline) occurred;
- change (from baseline) in Paco₂ ($\Delta_{\max30}$ Paco₂) and Pao₂ ($\Delta_{\max30}$ Pao₂) at $t_{\max30}$;
- printout of MPIAS screen display during whole study period.

We tried to ensure that the ABG changes recorded at $t_{\max30}$ were as a result of the change in oscillatory amplitude, by establishing a temporal relationship. This was achieved by recording the direction (+ or –) of change in Paco₂ and Pao₂ established before t_5 . The $t_{\max30}$ was calculated using this established directional change. If no change in baseline occurred before t_5 , this was also recorded, as it would be much less likely that subsequent ABG variations were due to the change in oscillatory amplitude. The FIO₂ at the time of the change in oscillatory amplitude (t_0) was recorded from the Sensormedics 3100A. Data were stratified into those from severe (FIO₂ > 0.4) and mild (FIO₂ < 0.3) lung disease groups depending on the FIO₂ at t_0 .

STATISTICAL ANALYSIS

Data from the high (FIO₂ > 0.4) and low (FIO₂ < 0.3) inspired oxygen groups were compared using Mann-Whitney U tests. Increases and decreases in oscillatory amplitude were compared separately. This stratified data into four groups. Where patients contributed more than one set of data to each group, the mean values were used. Thus individual patients contributed only one data point to each group. Data from oscillatory amplitude changes performed when FIO₂ was 0.3–0.4 were not included in the statistical analysis.

Table 1 Basic patient details and ventilation settings at t_0

	Increase in oscillatory amplitude		Decrease in oscillatory amplitude	
	High F_{IO_2}	Low F_{IO_2}	High F_{IO_2}	Low F_{IO_2}
No of patients	10	13	10	14
Birth weight (g)	1325 (690–2740)	1140 (400–2740)	1225 (690–2740)	1000 (400–2740)
Gestation (weeks)	29 (26–35)	27 (23–35)	29 (25–30)	27 (23–35)
Readings at t_0 :				
F_{IO_2} (%)	49 (40–80)	25 (21–30)	50 (40–100)	25 (21–29)
MAP (cm H_2O)	14.0 (12.2–16.2)	11.8 (8.5–13.8)	14.0 (11.1–18.5)	10.2 (8.5–13.2)
Amplitude (cm H_2O)	22 (20–33)	19 (14–30)	26 (24–38)	21 (16–32)
Δ amplitude (cm H_2O)	+2.9	+2.9	-2.7	-2.7
P_{aCO_2} (kPa)	6.00 (5.50–6.37)	5.81 (5.04–7.25)	4.55 (3.55–5.90)	4.32 (3.00–5.43)
P_{aO_2} (kPa)	8.9 (7.6–9.8)	7.7 (5.7–9.9)	7.9 (7.6–12.5)	8.7 (7.1–10.1)

Median (range) shown for variables in each group. MAP, mean airway pressure.

Results

We studied 21 infants of median (range) birth weight and gestation 1040 (400–2740) g and 27 (23–35) weeks respectively. Data were collected from 64 changes in oscillatory amplitude (33 decreases and 31 increases), including 12 random changes and excluding two changes where ABG went outside the acceptable range before the end of the study period. The data were stratified according to the F_{IO_2} at t_0 . This resulted in 33 changes in oscillatory amplitude in the low F_{IO_2} (< 0.3) group and 21 in the high F_{IO_2} (> 0.4) group. Table 1 summarises the basic data, including ventilator settings and blood gases at t_0 , for increases and decreases in oscillatory amplitude.

A comparison between infants in the high and low F_{IO_2} groups did not show any statistically significant differences for birth weight or gestation. However, there was a trend towards a longer gestation and higher birth weight in the high F_{IO_2} group, because most of these infants were rescued with HFOV rather than electively treated. As would be expected with more severe lung disease, infants in the high F_{IO_2} group also started each study period (t_0) with a higher mean airway pressure and oscillatory amplitude, although this was not statistically significant. Amplitude was changed in increments of ± 2 (n = 16) or ± 3 cm H_2O (n = 48). The mean change in amplitude does not differ between groups. No differences between the high and low F_{IO_2} groups were seen in the P_{aCO_2} or P_{aO_2} at t_0 . High P_{aCO_2} levels were seen before increases in oscillatory amplitude and low levels before decreases. This is to be expected as most of the ventilator changes were clinically determined.

CHANGES IN P_{aCO_2}

Table 2 and fig 1 summarise the changes in P_{aCO_2} seen following changes in oscillatory amplitude. After all changes in amplitude, the direction of change in P_{aCO_2} was established within five minutes of t_0 (and usually consider-

ably sooner). As expected, the main finding was that all increases in oscillatory amplitude resulted in a fall in P_{aCO_2} and all decreases in amplitude resulted in a rise in P_{aCO_2} (table 2). In the 30 minute study period, t_{max30} was 30 minutes in 62 of 64 of the amplitude changes. No statistically significant differences in $\Delta_{max30}P_{aCO_2}$ were seen between the high and low F_{IO_2} groups, although there was a slight trend to smaller changes in the high F_{IO_2} group. The magnitude of $\Delta_{max30}P_{aCO_2}$ was 0.87 kPa (range 0.52–1.60; n = 16) and 1.14 kPa (range 0.36–2.83; n = 48) for changes in amplitude of ± 2 cm H_2O and ± 3 cm H_2O respectively. This suggests a trend towards smaller changes in P_{aCO_2} with smaller changes in amplitude, but was not statistically significant.

In all 64 ABG traces obtained after changes in oscillatory amplitude, the change in P_{aCO_2} with time followed an exponential curve. Although the study period was 30 minutes, in most ABG traces P_{aCO_2} continued to change beyond t_{30} and data were collected until a new stable P_{aCO_2} baseline was clearly established. In nine of 64 ABG traces, either a further change in ventilator settings was clinically indicated or a new spontaneous change in the P_{aCO_2} occurred before a stable P_{aCO_2} could be established. In the remaining ABG traces (55 of 64), it was possible to identify the period when the P_{aCO_2} established a new stable baseline. The difference between the P_{aCO_2} at this period and t_0 enabled the total change in P_{aCO_2} after a change in oscillatory amplitude to be calculated. Thus the percentage of the total change in P_{aCO_2} that had occurred by any given time point could be established. Figure 1 shows the median percentage change at times t_5 , t_{10} , t_{20} and t_{30} for all patients. The most important clinical finding from these data is that 95.2% (90.6 to 99.7) of the change in P_{aCO_2} had occurred within 30 minutes of the change in oscillatory amplitude (median; 95% confidence interval for the median).

Table 2 Maximum change in P_{aCO_2} and P_{aO_2} in 30 minute study period ($\Delta_{max30}P_{aCO_2}$ and $\Delta_{max30}P_{aO_2}$).

	Increase in amplitude		Decrease in amplitude	
	High F_{IO_2}	Low F_{IO_2}	High F_{IO_2}	Low F_{IO_2}
No of patients	10	13	10	14
$\Delta_{max30}P_{aCO_2}$ (kPa)	-0.98 (-0.78, -1.47)	-1.13 (-0.84, -2.83)	+0.94 (+0.56, +1.28)	+1.24 (+0.57, +1.96)
$\Delta_{max30}P_{aO_2}$ (kPa)	0.0 (-0.6, +0.4)	+1.1 (+0.4, +4.7)	+0.2 (-0.2, +0.6)	-1.2 (-0.5, -2.1)

Median values (ranges) are shown. Mann-Whitney U tests were used to compare high and low F_{IO_2} groups. $\Delta_{max30}P_{aCO_2}$, no statistically significant differences; $\Delta_{max30}P_{aO_2}$: p < 0.001 for both increases and decreases in amplitude.

Figure 1 Graph showing percentage change in PaCO_2 with time following a change in oscillatory amplitude. Median values with 95% confidence intervals for the median are shown at each time point.

The exponential curve describing the percentage change in PaCO_2 (ΔPaCO_2) with time (t) in minutes fits the equation:

$$\Delta\text{PaCO}_2 = 100(1 - e^{-0.1t})$$

CHANGES IN PaO_2

Table 2 summarises the changes in PaO_2 seen following changes in oscillatory amplitude. The most important finding is that changes in oscillatory amplitude did affect PaO_2 in the low FiO_2 group but not in the high FiO_2 group. Increases in oscillatory amplitude resulted in a median rise of 1.1 kPa in the low FiO_2 group compared with 0.0 kPa in the high FiO_2 group ($p < 0.001$). Decreases in oscillatory amplitude resulted in a median fall of 1.2 kPa in the low FiO_2 group compared with a small rise of 0.2 kPa in the high FiO_2 group ($p < 0.001$).

All infants in the low FiO_2 group exhibited the same response: an increase in oscillatory amplitude resulted in a rise in PaO_2 , and a decrease in oscillatory amplitude resulted in a fall in PaO_2 . The change in PaO_2 occurred rapidly after the change in oscillatory amplitude. In this group, 31 of 33 changes in oscillatory amplitude resulted in a $t_{\text{max}30}$ for PaO_2 of less than 10 minutes (median = four minutes). More importantly, the direction of change in PaO_2 was established before t_5 in all 24 changes in oscillatory amplitude. Thus there appeared to be a consistent and temporal relation between the changes in oscillatory amplitude and PaO_2 .

In contrast, in the high FiO_2 group, there was no relation between the direction of change in oscillatory amplitude and the direction of the (small) change in PaO_2 . Only seven of 21 had a $t_{\text{max}30}$ of less than 10 minutes (median = 25 minutes), and in only seven of 21 was the direction of change in PaO_2 apparent before t_5 . This suggests that most of the changes in PaO_2 that were observed were not related to the change in oscillatory amplitude.

Figure 2 (A) Screen printout of multiparameter intra-arterial sensor (MPLAS) showing pH, PaCO_2 , and PaO_2 changes over a one hour period, in a 27 week gestation infant aged 9 hours. Previous chest radiograph confirmed moderate/severe respiratory distress syndrome, FiO_2 0.55. The vertical line marks t_0 when there was a 3 cm H_2O reduction in oscillatory amplitude. There is a subsequent rise in PaCO_2 (and corresponding fall in pH), but no change in the PaO_2 baseline. At the end of the study period, the PaO_2 falls sharply as FiO_2 is reduced to 0.45. (B) Screen printout of MPLAS showing pH, PaCO_2 , and PaO_2 changes over a one hour period, in the same infant 24 hours later. Previous chest radiograph confirmed improving respiratory distress syndrome, FiO_2 now 0.25. The vertical line marks t_0 when there was a 3 cm H_2O increase in oscillatory amplitude. There is a subsequent fall in PaCO_2 (and corresponding rise in pH). This is accompanied by a sharp increase in PaO_2 , completed in six minutes ($t_{\text{max}30}$), and sustained thereafter.

Most patients contributed data to either the high FiO_2 group or the low FiO_2 group. However, five of 21 contributed to both. Figure 2 shows the ABG traces of one of these patients. The first ABG trace shows the effects of changing the oscillatory amplitude with FiO_2 0.55 and the second with FiO_2 0.25. The same observation was made in all five patients contributing data to both FiO_2 groups. This indicates that the effects of changes in oscillatory amplitude are reproducible both within and between patients with differing severities of lung disease.

Some data were recorded ($n = 10$) when the FiO_2 was between 0.3 and 0.4. Our study design excluded data from this "intermediate" FiO_2 group in the statistical comparisons because we wanted to identify two distinct groups, one with severe and one with mild lung disease. The ABG traces obtained when the FiO_2 was 0.3–0.4 showed the same rapid change in PaO_2 after a change in oscillatory amplitude, but it

was not sustained. In most cases, P_{aO_2} returned to baseline within 10 minutes.

Discussion

This study describes in detail, for the first time, the effects of changes in oscillatory amplitude on P_{aCO_2} and P_{aO_2} in a clinical situation. Changes in oscillatory amplitude affect P_{aCO_2} by altering tidal volume.⁶ Tidal volume measurements during HFOV are difficult and are used as a research rather than a clinical tool. Experimental data from animal and computer models, together with clinical studies have tried to establish the relation between tidal volume and P_{aCO_2} .^{7–10–15} There are considerable differences in the relation between tidal volume, frequency, and P_{aCO_2} reported in these different studies. This has had limited clinical application, but has been used to establish changes in oscillatory amplitude as the method of controlling P_{aCO_2} in clinical practice.

Our findings confirm that increasing oscillatory amplitude (and so tidal volume) improves CO_2 elimination resulting in a fall in P_{aCO_2} . Decreases in amplitude have the opposite effect. We did not set out to quantify any relation between the magnitude of change in amplitude and the magnitude of change in P_{aCO_2} . The fact that no statistically significant differences were seen between changes in amplitude of ± 2 and ± 3 cm H_2O is not surprising given the wide variation in the magnitude of change in P_{aCO_2} .

We were able to describe the percentage change in P_{aCO_2} with time. This showed that about 95% of the change in P_{aCO_2} is completed within 30 minutes of the change in amplitude. This provides the definitive answer to the question: in infants receiving HFOV, how soon after a change in oscillatory amplitude should ABG sampling be performed? Our data also indicate that changes in amplitude of 2–3 cm H_2O will result in a median change in P_{aCO_2} of about 1.0 kPa. These are useful guidelines for clinicians managing infants without the benefit of continuous MPIAS monitoring. However, there is a wide range for $\Delta_{\max 30} P_{aCO_2}$ after similar changes in oscillatory amplitude, highlighting the dangers of managing infants receiving HFOV without some form of continuous CO_2 monitoring. Interestingly, major neonatal textbooks suggest ABG sampling 30–60 minutes after a change in conventional ventilator settings.¹⁶

Unexpectedly, we have shown that changing oscillatory amplitude does affect P_{aO_2} , but only in mild or improving lung disease with a low F_{IO_2} . Clearly, it is unlikely that the response in P_{aO_2} to a change in oscillatory amplitude is an all or none phenomenon based on high or low F_{IO_2} . This is confirmed by qualitative information from the patients who contributed to the “intermediate” F_{IO_2} group and those that contributed to both the high and low F_{IO_2} groups. Changes in P_{aO_2} start as a transient phenomenon lasting about 10 minutes. The P_{aO_2} then takes longer and longer to return to the baseline as the lung disease improves further. Eventually the P_{aO_2} shows a sustained

Key messages

- A 3 cm H_2O change in oscillatory amplitude results in a median change in P_{aCO_2} of about 1.0 kPa (but the range of effect is wide)
- Following changes in oscillatory amplitude:
 - the speed and direction of change in P_{aCO_2} is predictable;
 - about 95% of the change in P_{aCO_2} is completed within 30 minutes;
 - P_{aO_2} is unaffected if lung disease is severe;
 - if lung disease is mild/improving, rapid changes in P_{aO_2} occur (up to 4.7 kPa)

rise for the whole study period (fig 2B). This indicates that the effect of changes in amplitude on P_{aO_2} evolve as lung disease improves and F_{IO_2} falls.

Although this phenomenon needs further evaluation, it does suggest that the mechanisms governing gas exchange during HFOV change with the falling F_{IO_2} . There are two main reasons why F_{IO_2} can be reduced using the high lung volume strategy in HFOV. The first reduction in F_{IO_2} is associated with the recruitment of lung volume in the early phase of the high lung volume strategy. Further reductions in F_{IO_2} and ventilator settings result from improvements in lung disease. Five mechanisms of gas exchange in HFOV have been described,¹⁷ with the relative importance of each varying according to the region of the lung. Changes in the mechanical properties of the lungs may also alter the relation between the different modes of gas transport, and therefore the overall efficiency of HFOV. Such changes do occur with both changing lung volume^{18–19} and lung disease severity.^{7–20–21}

The changes in the mechanisms of gas exchange during HFOV that would explain the differing effects of oscillatory amplitude on P_{aO_2} are a matter of speculation. We have noticed that the change in P_{aO_2} with time is similar to that produced by altering F_{IO_2} . This would suggest that the change in P_{aO_2} may result from a change in alveolar PO_2 . One possibility is that the increase in lung compliance associated with improving lung disease means that bulk convection plays a more important role in gas exchange. Increasing oscillatory amplitude would increase direct alveolar ventilation and so alveolar PO_2 . Decreasing amplitude would have the opposite effect.

Whatever the mechanism of this phenomenon, the observed changes in P_{aO_2} following a change in oscillatory amplitude (up to 4.7 kPa) are clinically important. The clinician needs to be aware that improving lung disease and a falling F_{IO_2} in infants receiving HFOV indicate that changes in oscillatory amplitude will affect P_{aO_2} as well as P_{aCO_2} .

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